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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,558	09/15/2003	Qingbo Li	16969-053002	9049

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EXAMINER	
VATHYAM, SUREKHA	
ART UNIT	PAPER NUMBER
1753	
MAIL DATE	DELIVERY MODE
09/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,558	LI ET AL.	
	Examiner	Art Unit	
	Surekha Vathyam	1753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 06 July 2007.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 06 July 2007 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Drawings

1. The drawings were received on 6 July 2007. These drawings are acceptable.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1 – 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Each of independent claims 1, 9, 13 and 14 have been amended by applicant to include new limitations such as, "subjecting the nucleic acids to a second temperature sufficient to create a temporal gradient in at least the first portion" and "wherein the duration of the temporal temperature gradient approximates a migration rate of the nucleic acids through the first portion of the matrix". Applicant has pointed to several parts of the specification as originally filed, to support these limitations. However, the specification does not describe the explicit creation of a temporal gradient in the first portion and only discusses the temperature of the first portion to be a single value to be chosen from a range of values. In addition there is no description of a duration for the temperature application or of a migration rate of the

nucleic acids. There does not appear to be a written description of the claim limitations added to each of the independent claims.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 – 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of independent claims 1, 9, 13 and 14 recite the limitation, "wherein the duration of the temporal temperature gradient approximates a migration rate of the nucleic acids through the first portion". It is unclear how a "duration" (example, time) could approximate a "rate" (example, distance traveled over time). For purposes of examination, the claim will be interpreted to recite, "wherein the duration of the temporal temperature gradient approximates a migration <u>time</u> of the nucleic acids through the first portion" (emphasis added).

6. Claims 15 – 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 15, which depends from claim 14, recites the limitation, "the temperature". Claim 14 has at least two temperatures recited. It is unclear which of the two temperatures are being further limited by claims 15 – 19.

7. Claims 9 – 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Independent claim 9 recites "a portion of the matrix" in lines 3 –4 and line 8. However, lines 10 – 11 recite "the first portion". There is insufficient antecedent basis for "the first portion" in the claim.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1 – 2, 4 – 8 and 14 – 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karger et al. (US 5,633,129).

Regarding claim 1, Karger ('129) discloses a method of separating a first sample comprising nucleic acids (column 2, lines 19 – 21), the method comprising: providing a matrix that is essentially free of denaturing agents (column 5, lines 50 – 52); subjecting the nucleic acids to a first temperature in a first portion of the matrix (column 13, lines 1 – 6, column 13, lines 51 – 66 and column 14, lines 41 – 46); subjecting the nucleic acids to a second temperature sufficient to create a temporal gradient in the first portion (column 13, lines 56 – 60 and column 13, lines 64 – 66); subjecting the nucleic acids to electrophoresis through at least the first portion of the matrix (column 12, lines 49 – column 13, line 22); and deliberately cooling a second portion of the matrix (column 13, lines 54 – 58) to less than about 30 °C (column 13, lines 64 – 66 and column 13, lines 54 – 58), the nucleic acids migrating through the second portion after they have first migrated through the first portion (column 14, lines 54 – 59).

Karger ('129) does not explicitly disclose the duration of the temporal temperature gradient approximates a migration time of the nucleic acids through the first portion. However, Karger ('129) clearly discloses the temperature chosen for the temporal temperature gradient will depend upon the melting characteristic of the nucleic

acid, which in turn dictates it's migration time in the first portion of the matrix (column 13, lines 61 – column 14, line 23).

It would have been obvious to one of ordinary skill in the art to have chosen the optimum duration for the temporal temperature gradient to approximate a migration time of the nucleic acids as suggested by Karger ('129) (column 13, line 61 – column 14, line 23) because it would provide improved separation and enhanced resolution of the nucleic acids being electrophoresed.

Regarding claim 2, Karger ('129) discloses the method wherein the first portion of the matrix is raised to a temperature between 80 °C – 90 °C (column 13, lines 64 – 66).

Regarding claim 4, Karger ('129) discloses the method wherein the second portion of the matrix is cooled to less than about 25 °C (column 13, lines 64 – 66 and column 13, lines 54 – 58).

Regarding claim 5, Karger ('129) discloses the method wherein the matrix is completely free of denaturing agents (column 5, lines 50 – 52).

Regarding claim 6, Karger ('129) discloses the method further comprising subjecting a second sample of nucleic acids to electrophoresis within the same matrix, after the first sample has been electrophoresed (column 20, lines 18 – 22).

Regarding claim 7, Karger ('129) discloses the method comprising subjecting a total of at least 25 additional samples of nucleic acids, one at a time, without replacing the matrix (column 19, line 65 – column 20, line 1).

Regarding claim 8, Karger ('129) discloses the method wherein the temperature of at least a portion of the polymer matrix (column 14, lines 41 – 46) in which the second sample is electrophoresed is at least about 80 °C (column 13, lines 64 – 66).

Regarding claim 14, Karger ('129) discloses a method of separating a plurality of samples of biological compounds (column 23, lines 29 – 33), comprising: providing a matrix that is essentially free of denaturing agents (column 5, lines 50 – 52); subjecting a first sample to electrophoresis through said matrix (column 19, lines 61 – 65), the first sample comprising nucleic acids (column 19, lines 53 – 58), and wherein a temperature of a first portion of the matrix is sufficient to substantially denature the nucleic acids (column 19, lines 32 – 51 and fig. 8), and wherein a second temperature of the first portion of the matrix is sufficient to create a temporal gradient in said first portion (column 13, lines 56 – 60 and column 13, lines 64 – 66); and subjecting a second sample to electrophoresis in a separate step but through the same matrix (column 20, lines 18 – 36), the second sample comprising a complex of at least two biological compounds (column 19, lines 32 – 51 and column 20, lines 18 – 36).

Karger ('129) does not explicitly disclose the duration of the temporal temperature gradient approximates a migration time of the nucleic acids through the first portion. However, Karger ('129) clearly discloses the temperature chosen for the temporal temperature gradient will depend upon the melting characteristic of the nucleic acid, which in turn dictates it's migration time in the first portion of the matrix (column 13, lines 61 – column 14, line 23).

It would have been obvious to one of ordinary skill in the art to have chosen the optimum duration for the temporal temperature gradient to approximate a migration time of the nucleic acids as suggested by Karger ('129) (column 13, line 61 – column 14, line 23) because it would provide improved separation and enhanced resolution of the nucleic acids being electrophoresed.

Regarding claim 15, Karger ('129) discloses the method wherein the temperature is from about 80 °C to about 99 °C (column 13, lines 64 – 66).

Regarding claim 16, Karger ('129) discloses the method wherein the temperature is from about 80 °C to about 90 °C (column 13, lines 64 – 66).

Regarding claim 17, Karger ('129) discloses the method further comprising deliberately cooling a second portion of the matrix (column 14, lines 41 – 46) to less than about 30 °C (column 13, lines 64 – 66), the first and second samples migrating through the second portion after each has first migrated through the first portion (column 20, lines 18 – 22).

Regarding claim 18, Karger ('129) discloses the method wherein the second portion of the matrix is cooled to less than about 25 °C (column 13, lines 64 – 66).

Regarding claim 19, Karger ('129) discloses the method wherein the complex comprises at least one of a nucleic acid-protein complex and a protein-protein complex (column 23, lines 29 – 33).

12. Claims 3, 9 – 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karger et al. (US 5,633,129) in view of Chu et al. (US 6,770,698).

Karger ('129) discloses the method as discussed with regards to claim 1 above. Regarding claim 3, Karger ('129) discloses the matrix comprises at least one linear copolymer comprising a first comonomer of acrylamide (column 12, lines 38 – 45).

Karger ('129) does not explicitly disclose a secondary comonomer.

Chu ('698) teaches a random, linear copolymer (column 7, lines 35 – 38 and column 8, lines 44 – 55) comprising a first comonomer of acrylamide and at least one secondary comonomer (column 8, lines 61 – 65).

It would have been obvious to one of ordinary skill in the art to have modified the method of Karger ('129) to include the secondary comonomer taught by Chu ('698) because as Chu ('249) explains the copolymer formed as a result provides a more effective electrophoretic separation medium due to the difference in hydrophobicities of the two comonomers (column 8, lines 56 – 65).

Regarding claim 9, Karger ('129) discloses a method of separating a first sample comprising nucleic acids (column 2, lines 19 – 21), the method comprising: subjecting the nucleic acids to a first temperature in at least a portion of a matrix (column 13, lines 1 – 6, column 13, lines 51 – 66 and column 14, lines 41 – 46) that is essentially free of denaturants (column 5, lines 50 – 52), the matrix having at least one linear copolymer comprising a first comonomer of acrylamide (column 12, lines 38 – 45), subjecting the nucleic acids to a second temperature sufficient to create a temporal gradient in at least

a portion of the matrix (column 13, lines 56 – 60 and column 13, lines 64 – 66); subjecting nucleic acids to electrophoresis using said matrix (column 12, lines 49 – column 13, line 22).

Karger ('129) does not explicitly disclose a secondary comonomer and that the duration of the temporal temperature gradient approximates a migration time of the nucleic acids through at least a portion of the matrix. However, Karger ('129) clearly discloses the temperature chosen for the temporal temperature gradient will depend upon the melting characteristic of the nucleic acid, which in turn dictates it's migration time in the first portion of the matrix (column 13, lines 61 – column 14, line 23).

It would have been obvious to one of ordinary skill in the art to have chosen the optimum duration for the temporal temperature gradient to approximate a migration time of the nucleic acids as suggested by Karger ('129) (column 13, line 61 – column 14, line 23) because it would provide improved separation and enhanced resolution of the nucleic acids being electrophoresed..

Chu ('698) teaches a random, linear copolymer (column 7, lines 35 – 38 and column 8, lines 44 – 55) comprising a first comonomer of acrylamide and at least one secondary comonomer (column 8, lines 61 – 65).

It would have been obvious to one of ordinary skill in the art to have modified the method of Karger ('129) to include the secondary comonomer taught by Chu ('698) because as Chu ('249) explains the copolymer formed as a result provides a more effective electrophoretic separation medium due to the difference in hydrophobicities of the two comonomers (column 8, lines 56 – 65).

Regarding claim 10, Chu ('698) teaches comonomers are randomly distributed along the copolymer (column 7, lines 35 – 38 and column 8, lines 44 – 55), and wherein the at least one secondary comonomer is selected from the group consisting of vinyl monomers, monomers of acrylamide derivatives, monomers of acryloyl derivatives, monomers of acrylic acid derivatives, monomers of polyoxides, monomers of polysilanes, monomers of polyethers, monomers of derivatized polyethylene glycols, monomers of cellulose compounds, or mixtures thereof (column 8, lines 61 – 65), each having between 2-24 carbon atoms (column 5, lines 27 – 36).

Regarding claim 11, Chu ('698) teaches at least one secondary comonomer is N,N-dimethylacrylamide monomer (column 5, lines 35 – 36).

Regarding claim 12, Chu ('698) teaches the polymer is a copolymer polymerized using about a 1:1 ratio of acrylamide and N,N-dimethylacrylamide monomer (column 15, lines 43 – 46 and column 15, lines 51 – line 53).

Regarding claim 13, Karger ('129) discloses a method of sequencing a sample comprising nucleic acids (column 6, lines26 – 35), comprising: providing a matrix that is essentially free of denaturing agents (column 5, lines 50 – 52), the matrix having at least one linear copolymer (column 12, lines 38 – 45) comprising a buffer having a pH of at least about 8 (column 25, lines 37 – 43), subjecting the nucleic acids to a first temperature in at least a first portion of the matrix (column 13, lines 1 – 6, column 13, lines 51 – 66 and column 14, lines 41 – 46); and subjecting the nucleic acids to a second temperature sufficient to create a temporal gradient in at least the first portion

(column 13, lines 56 – 60 and column 13, lines 64 – 66); subjecting the nucleic acids to electrophoresis through said matrix (column 12, lines 49 – column 13, line 22); and prior to detecting the nucleic acids (column 14, lines 58 – 59), deliberately cooling a second portion of the matrix (column 13, lines 54 – 58) to less than about 25 °C (column 13, lines 64 – 66 and column 13, lines 54 – 58), the second portion of the matrix receiving nucleic acids from the heated portion of the matrix (column 14, lines 54 – 59).

Karger ('129) does not explicitly disclose the linear copolymer comprising about a 1:1 ratio of acrylamide and N,N-dimethylacrylamide monomer and that the duration of the temporal temperature gradient approximates a migration time of the nucleic acids through the first portion. However, Karger ('129) clearly discloses the temperature chosen for the temporal temperature gradient will depend upon the melting characteristic of the nucleic acid, which in turn dictates it's migration time in the first portion of the matrix (column 13, lines 61 – column 14, line 23).

It would have been obvious to one of ordinary skill in the art to have chosen the optimum duration for the temporal temperature gradient to approximate a migration time of the nucleic acids as suggested by Karger ('129) (column 13, line 61 – column 14, line 23) because it would provide improved separation and enhanced resolution of the nucleic acids being electrophoresed.

Chu ('698) teaches a random, linear copolymer (column 7, lines 35 – 38 and column 8, lines 44 – 55) comprising about a 1:1 ratio of acrylamide and N,N-dimethylacrylamide monomer (column 15, lines 43 – 46 and column 15, lines 51 – line 53).

It would have been obvious to one of ordinary skill in the art to have modified the method of Karger ('129) to include in the linear copolymer a 1:1 ratio of acrylamide and N,N-dimethylacrylamide monomer taught by Chu ('698) because as Chu ('698) explains the copolymer formed as a result provides a more effective electrophoretic separation medium due to the difference in hydrophobicities of the two comonomers (column 8, lines 56 – 65).

Response to Arguments

13. Applicant's arguments filed 6 July 2007 have been fully considered but they are not persuasive. Applicant remarks on page 8 of the response that "The present teachings disclose a vast temperature ramp that employs a temporal gradient whereby a capillary is exposed to a continuous temperature range". The specification as originally filed does not disclose a temperature ramp or a temporal gradient or a continuous temperature range. It instead discloses choosing a temperature value of at least 75 °C and provides temperature ranges from which the fixed temperature value is to be chosen (see specification page 9, lines 25 – 29). Karger ('129) on the other hand, contrary to applicant's assertion explicitly discloses a temperature gradient in the "denaturing zone" (column 13, lines 28 – 44) wherein the "denaturing zone comprises a portion of the channel in which the conditions cause the heteroduplexes to partially denature" (column 13, lines 3 – 6). Karger ('129) teaches heating a portion of the matrix which process would create a temporal temperature gradient (column 13, lines 56 – 58).

A gradient is defined as a change in the value of a quantity (such as temperature) per unit distance in a specified direction according to Webster's Third New International® Dictionary, Copyright © 1993. Karger ('129) expressly discloses a temperature gradient (column 13, lines 31 – 34) while no such disclosure is found in the applicant's specification.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Surekha Vathyam whose telephone number is 571-272-2682. The examiner can normally be reached on 7:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nam X. Nguyen can be reached on 571-272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SV/
20 September 2007

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